

REMARKS

Claims 68, 70-72, 75-80, 82-83, 85-96, 108-109, 111, and 115-126 are presently pending and under examination in the case. Claim 108 has been amended to correct an informality. No new matter is added by the amendment.

Applicant thanks the Examiner for withdrawing the finality of the previous rejection and reconsideration of the claims in the instant case. Applicant urges the Examiner to contact the Agent for Applicant listed below if the Examiner has any questions in relation to this response or believes that discussion of the response will facilitate the prosecution of the application.

Claim Objections

The Office Action has objected to claims 82 and 108 as being in improper form, each being dependent on the other. Claim 108 has been amended to depend from claim 81. The order of the claims is a result of the prosecution history of the application. Claim 82 was already pending on July 17, 2007 when claim was 108 added. As there is a prohibition against reordering of claims, the dependent claim must refer back to an earlier claim, rather than a later claim. Applicant requests that upon indication of allowable matter and renumbering of the claims at the close of prosecution that the Examiner reorder the claims such that the broader claims precede the narrower claims.

Rejection of claims under 35 U.S.C. §103

Withdrawal of prior rejections for obviousness

The Office Action has withdrawn the rejections over the combinations of Nemoto et al. (JP 03-240729) in view of Bhardwaj et al. (US 5,578,316) and Melia et al. (Aliment. Pharmacol. Therap. (1989) 3, 513-525); Nemoto et al. (JP 03-240729) in view of Bhardwaj et al. (US 5,578,316), Melia et al. (Aliment. Pharmacol. Therap. (1989) 3, 513-525) and Penkler et al.; and Nemoto et al. (JP 03-240729) in view of Bhardwaj et

al. (US 5,578,316), Melia et al. (Aliment. Pharmacol. Therap. (1989) 3, 513-525) and Olinger et al. No amendments were made in response to the rejections.

The rejections all relied upon the alleged teachings of Nemoto to provide a composition comprising an active substance with a low solubility in combination with an alkaline substance to provide a particulate composition having a mean particle size larger than claimed in the instant invention. In each case, the Office Action relied on Melia, which teaches API size and not particle size, to provide motivation to reduce the particle size taught by Nemoto to arrive at the instant invention. As there is no motivation to reduce the particle size based on the teachings of Melia, the rejections were withdrawn.

Although not noted in the instant Office Action, the rejection of claims in view of the combination of Nemoto, Bhardwaj, Melia, and Kloize from the prior Office Action was also withdrawn and replaced by the rejections in view of Nemoto and Kloize in the instant Office Action. The prior rejection stated that:

One of ordinary skill in the art would do this [reduce granule size to 149 μ M to 840 μ M] because the modification of granule particle size would have been obvious during the process of routine experimentation, as evidenced by the surface area increase, and consequently, the dissolution rate increase, as evidenced by Melia. (Office Action mailed June 30, 2009; page 16, emphasis added)

As discussed in the prior response, and as acknowledged by the withdrawal of the rejections above, Melia cannot provide motivation to reduce granule size as Melia teaches API size. There can be no motivation to combine Nemoto and Kloize, either with or without the teachings of Melia. The prior rejection would not have included Melia if the combination of references could have been made without Melia. The new rejection of the claims in view of Nemoto and Kloize with or without Penkler should be withdrawn as there can be no motivation to combine the references.

New rejections for obviousness

The Office Action has newly rejected the claims over Nemoto (JP 3-240729) in view of Kloize (US Patent 2,887,439); and over Nemoto in view of Kloize and Penkler (US Patent 5,854,226). The rejections will be addressed simultaneously.

Dissolution rate is not the same as disintegration rate

Nemoto is relied upon to teach a composition comprising an active substance with a low solubility in combination with an alkaline substance to provide a particulate composition having a mean particle size of larger than claimed in the instant invention. Kloize is relied upon to teach the use of granules of the instantly claimed size. The Office Action states that:

one of ordinary skill in the art would make the granules taught by Nemoto and modify the granule size based on the teaching of Kloize that granules from 149 μ M to 840 μ M can be tableted into **rapidly disintegrating tablets**. (page 4, emphasis added)

The instantly claimed invention is not directed to tablets with a specific disintegration rate. The claims are directed to tablets with a specific **dissolution rate**. Nemoto is not concerned with disintegration rate. Nemoto is concerned with a **dissolution rate**. Kloize is not concerned with a dissolution rate. Kloize is concerned with a **disintegration rate**.

Disintegration is concerned with particles falling apart, not releasing an active agent. Dissolution is concerned with the active agent being in solution. As noted in *Remington's Pharmaceutical Sciences*, 16th Edition (see page 1559-60, copy enclosed), disintegration rate and dissolution rate are independent of each other.

In a comparison of disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster absorbed tablets had the longer disintegration time.

Applicant notes that this distinction between disintegration and dissolution was also made in the first paragraph of Melia. One would not look to a reference teaching dissolution rates to alter disintegration rates, or vice versa. For this reason alone, the

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rejection should be withdrawn. However, in the event that the argument is not found persuasive, Applicant provides the further remarks in relation to the rejection.

Nemoto and Kloize must be considered for what they teach as a whole

Applicant notes that both the Kloize and Nemoto references are related to making tablets and both references discuss manufacturing considerations important in the process of making tablets. Modification of either of the references to make a composition not appropriate for tableting cannot be obvious as such a modification would make each reference unsuitable for its intended purpose.

Throughout Kloize, the importance of sufficient granule size for tableting is discussed. For example, Kloize includes the following statements:

Upon completion of the drying, the granules are preferably screened, to insure that they are of an optimum size for the formation of tablets. It has been found that granules ranging from about 20 mesh to 100 mesh (U.S. Sieve Series) are most advantageous in preparing tablets for the invention.

After drying and screening of all of the granules, they are blended together in the appropriate proportions for tableting purposes. During this blending operation... care being taken not to introduce a large proportion of finely divided material, since this would impair the tableting operation. It may be desired, for instance, to add minerals or vitamins already in granular form... This may be incorporated in separate granules, or most conveniently included in either the antihistamine-containing granules or the sweetener-containing granules. (col. 2, lines 41-63, emphasis added)

The dried blend was then passed through a 20-mesh [0.853 mm] stainless steel screen... retaining all granules that passed through a 30-mesh [0.599 mm] screen....

Portion B was thoroughly blended and milled.... One-fourth of this was then wetted with 66% isopropanol-water solution... and then passed through a 20 mesh screen... Fines that passed through a 100-mesh [0.152 mm] screen on the separator were recycled.

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The remaining three-fourths of the blended portion B was granulated in the same way as the first one-fourth. (col. 4, lines 24-38, emphasis added)

Therefore, although Kloize does teach that granules ranging in size from 20-mesh to 100-mesh are advantageous for preparing, that is manufacturing, tablets, Kloize teaches that **particles smaller than 100-mesh should be discarded** and that care must be taken to prevent formation of finely divided material.

Therefore, taken as a whole, Kloize would have been understood at the time of filing of the instant application to teach that:

1. Active agents for incorporation into tablets should be granulated (i.e., API should be made into larger, more homogeneously sized particles).
2. Granule size is important for manufacturing considerations, not for drug delivery considerations.
3. Granules in the range of 0.853-0.152 mm can be used for preparation of tablets, however particles on the larger end of the scale are typically used. Particles smaller than 0.152 mm should be removed prior to the formation of tablets as an excess of finely divided material results in difficulties during the tabletting process.

The reference must be taken as a whole. Despite the teaching that smaller granules can be used for the preparation of tablets, larger granules are preferred (see the one working example in column 4 quoted above). One reading the reference as a whole would not suggest to one of skill in the art at the time of filing of the instant application to use a smaller granule size.

Similarly, the use of smaller granules in the claimed range cannot be obvious in view of Nemoto. Nemoto teaches that although the combination of anti-inflammatory agents with antacids is useful for increasing solubility of the anti-inflammatory agent, the amount of antacid added must be carefully titrated to insure that the mixture can be

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properly granulated for preparation of tablets. Specifically, in the last paragraph on page 2, Nemoto states that:

For example, in the case of tablets, solubility is improved by blending at least 1 part by weight of sodium hydrogen carbonate to 1 part by weight of chlortenoxicam, and if 10 parts by weight or more are blended, solubility is improved significantly. However, if more than 20 parts by weight are blended, hardness decreases thereby preventing suitable tablets from being obtained, and if more than 15 parts by weight are blended, the tablets are subject to problems in terms of forming such as cracking or chipping during coating. (emphasis added)

That is, per the teachings of Nemoto, solubility and hardness are manipulated predictably by changing ratios of various components of the tablets. If Nemoto were concerned only with dissolution, Nemoto would simply increase the amount of antacid. However, as the formulation has no use if it cannot be made into a pharmaceutical dosage form, Nemoto must manipulate the formulation to provide a composition appropriate for tableting.

Similarly, Nemoto is concerned with having appropriate granule size to promote flow. Changes in flow properties of granules are predictably modified by manipulation of ratios of various components of formulations. On page 3, Nemoto states:

On the other hand, in the case of granules, it is preferable to blend 20-40 parts by weight of aluminium magnesium metasilicate to 1 part by weight of chlortenoxicam, and more preferably 15-30 parts by weight of aluminium magnesium metasilicate. If more than 40 parts by weight are blended, however, granulation becomes difficult, thereby preventing the production of granules that have good fluidity. In addition in the cases of sodium hydrogen carbonate, although solubility is improved by blending at least 1 part by weight of sodium hydrogen carbonate to 1 part by weight of chlortenoxicam, if more than 20 parts by weight are blended, the ease of forming of the granules becomes poor causing the surface of the granules to chip during coating. (emphasis added)

Therefore, solubility and hardness of granules are manipulated predictably by changing ratios of various components of the formulations. Formulations that are hard to granulate are not desirable.

Nemoto prepares 11 different formulations for tabletting. All are made by the same method after combining the ingredients. Three of the granule formulations for tabletting are used to fill capsules. In all cases, the method for granulation of the material is the same.

Therefore, one reading Nemoto in view of Kloize would not be inclined to use smaller granules, or to modify the size or method for making granules as each provides only a single method for making tablets (although the tablets of Kloize do include granules of different sizes). The formulations of Nemoto with better solubility were more fragile. Such formulations were considered unacceptable for pharmaceutical preparations. Kloize teaches that care should be taken "not to introduce a large proportion of finely divided material, since this would impair the tabletting operation." As discussed in the references cited in the Office Action, the use of sufficiently large granules and the absence of fines are important for the production tablets as in Nemoto and Kloize. For these reasons, based on the teachings of Kloize and Nemoto, one could not arrive at the instantly claimed invention in which "the particles of the particulate composition used in the manufacture of the composition have a mean particle size of at the most 250 micrometers, or at least 50% w/w of the particles of the particulate composition used in the manufacture of the composition pass through a 180 micrometer sieve."

Nemoto and Kloize must be considered in view of the totality of the art at the time of filing of the instant application

Applicant has provided multiple references throughout the prosecution of the instant application to demonstrate that one of skill in the art would not consider reduction of granule size or the use of granules of the sizes claimed to be advantageous in the preparation of pharmaceutical compositions. Despite these references, the Office Actions have maintained the position that it would be obvious to modify Nemoto to provide the instantly claimed invention.

The fact pattern in the instant case are similar to that in *In re Hedges*, et al., 228 USPQ 685 (Fed. Cir. 1986). In *In re Hedges*, the claims were directed to carrying out a

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chemical reaction at an elevated temperature, above the melting temperature of one of the components (in excess of 110°C). The claims were rejected by the Examiner and the Appeal Board for allegedly being obvious in view of the Felix reference which taught the reaction at a lower temperature, about 5-10°C, with the temperature rising due to the endothermic nature of the reaction to about 30°C. This was substantially lower than the temperature claimed by Hedges. The Court discussed the prosecution of the application, and the rejections of the claims in view of the cited art.

To overcome this deficiency in Felix [related to reaction temperature] the Solicitor directs attention to the British patent, which discusses the reaction of liquid phenols with liquid sulfur trioxide in the absence of a solvent. The PTO points to the teachings of reaction at elevated temperature:

The invention is applicable to liquid and solid phenols . . . having melting points up to 115°C . . . and to mixtures of phenols whose individual melting point is higher than 115°C but which give in admixture a melting point of 115°C or lower.

For mono-sulphonic acids . . . the temperature is kept above the melting point of the phenol used.

. . . the liquid sulphur trioxide is added . . . at a temperature slightly above the melting point of the phenol in the case of solid phenols, and after the addition the reaction mass is heated at a higher temperature of 160-180°C. . . .

The highest-melting phenol illustrated in the British patent is resorcinol, melting point 110°C, to which

liquid sulfur trioxide is added . . . at a temperature of 115-140°C. . . . **The product, which is almost black in colour and sets to a brittle solid on cooling,** is substantially the monosulphonic acid in quantitative yield.

The Solicitor asserts that this shows that aromatic compounds can be sulfonated, in the absence of solvent, in the molten state, at the temperatures contemplated by Hedges. Hedges argues that the British patent expressly teaches that the reaction cannot be carried out with phenols that melt higher than 115°, that the upper temperature range reported for resorcinol is reached during the exothermic reaction, and that the black color and brittle product are due to charring and decomposition.

Hedges argues that the British patent does not negate the overall teachings of the art as a whole that lower temperatures are preferred for optimum results, and that the charring at higher temperatures that is shown in the British patent belies the broad conclusion that the Solicitor attempts to draw. The cited references support Hedges' position. (*Id.* at 687, emphasis added)

Therefore, although a reaction similar to that of Hedges had been carried out at a higher temperature, the reaction product was not satisfactory. Therefore, despite the existence of all of the elements in the cited art, one of skill would not have performed the steps of Felix at the higher temperature as the product was unsatisfactory, and the teachings were contrary to the teachings of the art as a whole.

Hedges argues that he sulfonates liquid diphenyl sulfone at high temperature without the expected charring or reduced yields, and that "**the totality of the prior art disclosures leads substantially away from the claimed invention**". We agree with Hedges that the prior art as a whole must be considered. **The teachings are to be viewed as they would have been viewed by one of ordinary skill.** *Kimberly-Clark v. Johnson & Johnson*, 745 F.2d 1437, 1454, 223 USPQ 603, 614 (Fed.Cir. 1984); *In re Mercier*, 515 F.2d 1161, 1165, 185 USPQ 774, 778 (CCPA 1975). (*In re Hedges*, at 686, emphasis added)

It is the same in the instant case, the totality of the prior art disclosures, both the entire references relied upon in the rejection and the references provided by Applicant to demonstrate the state of the art, must be considered as a whole and viewed as they would have been viewed by one of ordinary skill. When the art is considered as a whole, there can be no motivation to use smaller granules as instantly claimed. In *In re Hedges*, the Court further noted that the picking and choosing phrases from a reference to support a position contrary to the teachings of the reference as a whole is not permitted. Specifically, the Court cited the earlier *In re Wesslau* decision which stated:

"It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In re Wesslau*, 353 F.2d at 241, 147 USPQ at 393. Hedges correctly points out that the references all suggest that lower temperatures of reaction are preferable. ...The data provided by Hedges

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show significant advantages of the claimed invention; these data are not challenged by the PTO. (*In re Hedges*, at 687, emphasis added)

The reliance of the rejection on two lines of Kloize in view of the teachings of the reference as a whole does not show a full appreciation of what such a reference fairly suggests to one of ordinary skill in the art. It was noted in *In re Hedges*, that

On balance, Hedges proceeded contrary to the accepted wisdom. This is “strong evidence of unobviousness”. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 USPQ 303, 312 (Fed.Cir. 1983), cert. denied, 105 S.Ct. 172 (1984), citing *United States v. Adams*, 383 U.S. 39, 148 USPQ 479 (1966). (*Id.*, at 687)¹

Applicant submits that the instantly claimed invention is contrary to the accepted wisdom and is not obvious in view of the cited art. Therefore, the instantly claimed invention must be non-obvious.

In considering a reference in an obviousness rejection, one must consider what the reference would have made obvious to one of skill in the art at the time of filing of the application. The Kloize patent issued in 1959 based on an application that was filed in 1956. Nemoto was filed on February 14, 1990. Tablets were formed by Nemoto using a tablet forming machine (top of page 6). Therefore, when making tablets based on the teachings of Nemoto, one would look to tablet forming machines and technologies available to Nemoto, not tablet forming methods of Kloize. Therefore,

¹ “Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*” provided in the *Federal Register*, Vol. 72, No. 195, pp. 57526-35, cites *United States v. Adams* and provides the following footnote (p. 57592)

United States v. Adams, 383 U.S. 39, 51–52, 148 USPQ 479, 483 (1966). In Adams, the claimed invention was to a battery with one magnesium electrode and one cuprous chloride electrode that could be stored dry and activated by the addition of plain water or salt water. Although magnesium and cuprous chloride were individually known battery components, the Court concluded that the claimed battery was nonobvious. The Court stated that “[d]espite the fact that each of the elements of the Adams battery was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore” the teaching away of the prior art that such batteries were impractical and that water-activated batteries were successful only when combined with electrolytes detrimental to the use of magnesium electrodes. (emphasis added)

considerations such as good flow to allow proper filling noted by Nemoto must be considered.

The instant application is based on a priority application filed in 1998. Applicant submits that one of skill in the art would not likely to rely on a reference from forty years earlier when considering the field of preparation of pharmaceutical compositions. Instead, one of skill in the art would look to a reference more contemporary to the filing date of the application, particularly in regard to manufacturing considerations which would be expected to have changed somewhat in forty years.² Applicant acknowledges that although the age of a reference is not a sufficient reason to assert that it cannot be properly applied to the claims or combined with a later reference, the rejection must consider what would have been obvious to one of skill in the art at the date of filing the application. Therefore one must consider if in the field of pharmaceutical science one would be motivated to look back thirty to forty years for motivation to modify tablet preparation. As an example, Applicant points to the photograph on page 1564 of Remington's Pharmaceutical Sciences, 16th Edition (1980) to show the "first large-scale computer controlled tablet manufacturing facility." The image is nearly comical now. It clearly illustrates the changes in pharmaceutical manufacturing practices that have occurred in the last thirty years since the publication of that edition. However, concerns related to more automated methods of pharmaceutical preparation are generally relevant today. The importance of the pharmaceutical formulations having good flow and compressible characteristics has not changed and are discussed on the same page as the photograph. As discussed above, reducing granule size would provide material less desirable for tableting. Decreasing the granule size of Nemoto to the size instantly claimed would likely result in poor flow characteristics, resulting in tableting difficulties.

Applicant points to the following references previously cited in the prosecution of the instant application to demonstrate particle sizes typically used in the preparation of tablets:

² References cited in the prosecution of Kloize include Remington's Practice of Pharmacy, 9th Edition, demonstrating that the reference was considered to show the state of the art at the time of filing the Kloize application. Applicant cites later versions of Remington's to demonstrate the state of the art closer to the time of filing the instant application.

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1. Lieberman et al., *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc. c. 1990, Second Edition, volume 2, pages 33-34 (cited in response filed September 28, 2009)

On page 33, a preference for the use of particles greater than 60 mesh (0.251 mm) for their improved flow properties is noted, as well as the difficulties of using particles of less than 100 mesh in size.

The table on top of page 34 of Lieberman, as the particle size decreases relative to surface area, the effects of the surface forces are amplified, increasing problems with flow of materials having a particle size of 75 μM -200 μM . By increasing the mass of the particle to the surface area, the problems of surface forces are decreased. Particles having a size of < 100-75 μM have problems with flow due to both surface energy forces and static electrical forces.

2. *Remington's Pharmaceutical Sciences*, 16th Edition (c. 1980) and 21st Edition (c. 2006) (cited in response filed September 11, 2008). Herein, the 15th Edition (1975) is also cited and appropriate pages are provided.

On page 1586 of the 15th Edition, on page 1563 of the 16th Edition, and on page 898 of the 21st Edition, a table is presented showing that granule size is selected based on the final size of the tablet.

On page 1563 of the 16th Edition, left column, the importance of maintaining granule size and the minimization of fines is discussed to facilitate tablet preparation, to insure an even fill, and to provide tablets with an appropriate hardness.

On pages 1595 to 1596 of the 15th Edition, on pages 1572 to 1573 of the 16th Edition, and on pages 912-913 of the 21st Edition, tablet formulations are provided. Mesh sizes of 12 (1.4 mm) to 20 are used. No higher mesh sizes to provide smaller particles are used.

Applicant notes that all of the references cited in the instant rejection and by Applicant to demonstrate the state of the art discuss particle size as a manufacturing consideration. All of the references caution against the use of particle sizes that are too

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small. Therefore, based on the teachings of the references, one of skill in the art could not be motivated to decrease particle size based on manufacturing considerations.

Granule size is not a result-effective variable for dissolution

The Office Action asserts that “one of ordinary skill in the art would make the granules taught by Nemoto and modify the granule size based on the teaching of Kloize that granules from 149 μ M to 840 μ M can be tableted into rapidly disintegrating tablets.” As discussed above, granule size is not directly correlated to disintegration or dissolution rates, therefore the rejection must fail. Further, the rejection suggests that granule size is considered in the Office Action to be a result-effective variable. The Examiner has failed to provide a reference demonstrating that one of skill in the art would understand granule size to be a result-effective variable in relation to dissolution. In fact, the text cited from *Remington's Pharmaceutical Sciences*, 16th Edition (see page 1559-60) above states that the aspirin tablets having the faster dissolution rate had the slower disintegration rate. **This demonstrates that one of skill in the art would know that granule size was not a result effective variable for dissolution.**

In the absence of some demonstration that granule size would be considered to be a result-effective variable in relation to dissolution, the rejection must fail. In *In re Antonie* (195 USPQ 6 (C.C.P.A. 1977) 195 USPQ 6) the court noted that:

In *In re Aller*, 42 CCPA 824, 220 F.2d 454, 105 USPQ 233 (1955), the court set out the rule that the discovery of an optimum value of a variable in a known process is normally obvious. We have found exceptions to this rule in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good. *In re Waymouth*, 499 F.2d 1273, 182 USPQ 290 (CCPA 1974); *In re Saether*, supra. **This case, in which the parameter optimized was not recognized to be a result-effective variable, is another exception.** The decision of the board is reversed. (at 8-9, emphasis added)

In the instantly claimed invention, the parameter optimized was not recognized to be a result-effective variable. Therefore, it is an exception to the rule that optimization of a value of a variable is routine experimentation. Modulation of dissolution properties by modulation of granule size is not routine. Therefore, the invention cannot be obvious.

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Penkler does not overcome the deficiencies of the rejection as set forth above.

In summary, the rejection fails for at least the following reasons.

First, Kloize is concerned with tablet disintegration, not with tablet dissolution as in Nemoto. For at least this reason there can be no motivation to combine the references.

Second, when taken as a whole, both references caution against the use of smaller granules. These teachings are supported by references provided by Applicant to demonstrate the knowledge of one of skill in the art. Nemoto teaches compositions that are inherently fragile. The use of smaller granules rather than larger granules would have been contrary to the teachings of Nemoto, and contrary to the general teachings of the art. Proceeding contrary to the teachings of the art is evidence of non-obviousness. Therefore, the claimed invention cannot be obvious.

Third, a reference must be understood for what it would have taught one of skill in the art at the time of filing of the application. One of skill in the art of preparation of pharmaceutical compositions would not likely look back forty years for suggestions on how to modify compositions in modern manufacturing equipment. Therefore, the claimed invention cannot be obvious.

Fourth, granule size is not a result-effective variable for dissolution or disintegration. Optimization of a parameter not known to be a result-effective variable is not obvious. Therefore, the claimed invention cannot be obvious.

It is believed that there is no fee due with this response. However, if a fee is due with this paper or any other paper filed by this firm in relation to this application, Applicant hereby authorizes the Commissioner to charge Deposit Account No. 04-1105 citing Docket No. 55682CON(71432). Credit of any overpayment is respectfully requested.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance. However, if the Examiner believes that there

are any outstanding issues in the case that could be addressed by a telephone interview, the Examiner is encouraged to call the Agent for Applicant listed below.

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Respectfully submitted,

Electronic signature: /Colleen McKiernan/
Colleen J. McKiernan, Ph.D.
Registration No.: 48,570
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617)517-5555
Attorneys/Agents For Applicant
Customer No.: 21874